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Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease
A Systematic Review and Meta-analysis

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IMPORTANCE Timing of introduction of allergenic foods to the infant diet may influence the risk of allergic or autoimmune disease, but the evidence for this has not been comprehensively synthesized.

OBJECTIVE To systematically review and meta-analyze evidence that timing of allergenic food introduction during infancy influences risk of allergic or autoimmune disease.

DATA SOURCES MEDLINE, EMBASE, Web of Science, CENTRAL, and LILACS databases were searched between January 1946 and March 2016.

STUDY SELECTION Intervention trials and observational studies that evaluated timing of allergenic food introduction during the first year of life and reported allergic or autoimmune disease or allergic sensitization were included.

DATA EXTRACTION AND SYNTHESIS Data were extracted in duplicate and synthesized for meta-analysis using generic inverse variance or Mantel-Haenszel methods with a random-effects model. GRADE was used to assess the certainty of evidence.

MAIN OUTCOMES AND MEASURES Wheeze, eczema, allergic rhinitis, food allergy, allergic sensitization, type 1 diabetes mellitus, celiac disease, inflammatory bowel disease, autoimmune thyroid disease, and juvenile rheumatoid arthritis.

RESULTS Of 16 289 original titles screened, data were extracted from 204 titles reporting 146 studies. There was moderate-certainty evidence from 5 trials (1915 participants) that early egg introduction at 4 to 6 months was associated with reduced egg allergy (risk ratio [RR], 0.56; 95% CI, 0.36-0.87; I^2 = 36%; P = .009). Absolute risk reduction for a population with 5.4% incidence of egg allergy was 24 cases (95% CI, 7-35 cases) per 1000 population. There was moderate-certainty evidence from 2 trials (1550 participants) that early peanut introduction at 4 to 11 months was associated with reduced peanut allergy (RR, 0.29; 95% CI, 0.11-0.74; I^2 = 66%; P = .009). Absolute risk reduction for a population with 2.5% incidence of peanut allergy was 18 cases (95% CI, 6-22 cases) per 1000 population. Certainty of evidence was downgraded because of imprecision of effect estimates and indirectness of the populations and interventions studied. Timing of egg or peanut introduction was not associated with risk of allergy to other foods. There was low- to very low-certainty evidence that early fish introduction was associated with reduced allergic sensitization and rhinitis. There was high-certainty evidence that timing of gluten introduction was not associated with celiac disease risk, and timing of allergenic food introduction was not associated with other outcomes.

CONCLUSIONS AND RELEVANCE In this systematic review, early egg or peanut introduction to the infant diet was associated with lower risk of developing egg or peanut allergy. These findings must be considered in the context of limitations in the primary studies.

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Supplemental content

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Increasing attention has focused on the role of timing of introduction of allergenic food into the infant diet and risk of allergic and autoimmune diseases. Infant feeding guidelines have moved away from advising parents to delay the introduction of allergenic food, but most guidelines do not yet advise early feeding of such foods.[1-3] Several professional organizations have responded to recent research findings by issuing interim guidance advising early peanut introduction in infants at high risk of peanut allergy, with some caveats.[4,5] However, a randomized clinical trial of early introduction of multiple allergenic foods did not show efficacy for preventing food allergy,[6] and a trial of early gluten introduction showed no effect on risk of celiac disease.[7] The implications for preventing food allergy or other immune-mediated health conditions in the general population are not clear.

To inform UK infant feeding guidance, we undertook a systematic review and meta-analysis for the UK Food Standards Agency, evaluating whether timing of allergenic food introduction to the infant diet influences risk of allergic or autoimmune disease. This is one of a series of systematic reviews of dietary exposures in pregnancy or infancy and immune outcomes, the first of which reviewed hydrolyzed infant formula.[8] The immunological mechanisms underlying the different allergic and autoimmune diseases vary. For example, most food allergy is characterized by IgE-mediated inflammation, whereas type 1 diabetes mellitus is caused by T cell-mediated islet cell destruction.[9,10] However, these diseases share a common feature of impaired immune tolerance, and immune function in infancy may be modified by dietary exposures. Therefore, a comprehensive range of allergic and autoimmune outcomes were included.

Key Points

Question Does the timing of allergenic food introduction to infants affect their risk of developing allergic or autoimmune disease?

Findings There was moderate-certainty evidence that early introduction of egg (from 4-6 months) or peanut (from 4-11 months) was associated with reduced risk of egg or peanut allergy, respectively. There was low- to very low-certainty evidence that early fish introduction was associated with reduced allergic sensitization and rhinitis and high-certainty evidence that timing of gluten introduction was not associated with risk of celiac disease.

Meaning Early introduction of egg or peanut to infants was associated with a reduced risk of egg or peanut allergy.

Methods and Literature Search

Methods are described in the Supplement. This systematic review is reported according to PRISMA guidance.[11] We searched the Cochrane Library, EMBASE, LILACS, MEDLINE, Web of Science, and http://apps.who.int/trialsearch from January 1, 1946, to March 8, 2016. Intervention trials and observational studies evaluating age at allergenic food introduction (milk, egg, fish, shellfish, tree nuts, wheat, peanuts, soya)[12] during the first year and allergic or autoimmune disease at any age were included. Other systematic reviews rated as high quality using published criteria[13] were also included per the study protocol to avoid duplicating existing work. When other systematic reviews were included, original studies that were not captured by the other reviews were also summarized. Outcomes evaluated were wheeze, eczema, allergic rhinitis, food allergy (a reproducible hypersensitivity reaction to a food), allergic sensitization (the presence of specific IgE to an allergen), type 1 diabetes mellitus, celiac disease, inflammatory bowel disease, juvenile rheumatoid arthritis, psoriasis, and vitiligo.

Data were extracted in duplicate and risk of bias assessed using the Cochrane Risk of Bias tool and the National Institute for Clinical Excellence methodological checklists for intervention and observational studies, respectively. Publication bias was assessed using funnel plots and the Egger test when meta-analyses included at least 10 studies. Random-effects meta-analyses used generic inverse variance and Mantel-Haenszel methods for observational and intervention studies, respectively. Heterogeneity was quantified using the I^2 statistic. Meta-analyses with I^2>80% were not pooled. For meta-analyses with more than 5 studies, we explored heterogeneity in prespecified subgroup analyses of study design, risk of bias, risk of conflict of interest, and features of the population, intervention, and outcome assessment. For meta-analyses with 5 or fewer studies, we explored statistical heterogeneity descriptively and also conducted sensitivity analyses by study design and risk of bias for the key review findings. The statistical program used for meta-analysis was R, version 3.1.0 (R Project), and statistical significance was set at 2-sided P<.05.

Post hoc trial sequential analysis was used to quantify statistical reliability of moderate- or high-certainty review findings using a 2-sided P<.05 significance level, 80% power, and control event rates from included studies to estimate optimal heterogeneity-adjusted and unadjusted information sizes needed to identify relative risk reductions of 10%, 20%, and 30%. Trial sequential analysis quantifies statistical reliability of data in a cumulative meta-analysis in a similar way to an interim analysis in a single randomized clinical trial. GRADE was used to assess certainty of evidence, and the protocol was registered in PROSPERO.[14] Ethical approval was not required by the Imperial College Joint Research Office. The data set and statistical code are available from the corresponding author.

Results

Search results are summarized in eFigure 1 (existing systematic reviews) and eFigure 2 (original studies) in the Supplement. A summary of the findings of the 2 included systematic reviews is shown in eTables 1 and 2 in the Supplement.

Title, abstract, and full-text screening of original studies yielded 146 eligible studies (204 separate titles). Overall, 24 intervention trials (39 titles) evaluated allergic outcomes in 13 298 participants and 5 intervention trials (6 titles) evaluated autoimmune diseases in 5623 participants. Sixty-nine

observational studies (90 titles) reported allergic outcomes in 142 103 participants and 48 observational studies (69 titles) evaluated autoimmune diseases in 63 576 participants. No study reported psoriasis or vitiligo. For allergic outcomes, these included 55 cohort studies (1 retrospective), 2 nested case-control studies, and 12 case-control or cross-sectional studies. For autoimmune diseases, there were 7 cohort studies, 4 nested case-control studies, and 37 case-control studies. Characteristics of included studies are summarized in eTables 3 and 4 (allergic outcomes) and eTables 5 and 6 (autoimmune outcomes) in the Supplement. More detailed characteristics of the intervention studies of egg or peanut introduction that reported egg or peanut allergy are shown in **Table 1** and **Table 2**.

Risk of bias was low in 4 (17%) of 24 intervention trials and 29 (42%) of 69 observational studies for allergic outcomes (eTables 7 and 8 in the Supplement), and in 1 (20%) of 5 intervention trials and 10 (21%) of 48 observational studies for autoimmune outcomes (eTables 9 and 10 in the Supplement). The main issues identified were attrition bias in intervention trials and lack of adjustment for potential confounders in observational studies.

The key findings of the systematic review are summarized in **Table 3**, with GRADE evidence assessment summarized in **Table 4** and specific analyses for all positive or high-certainty findings shown in **Figure 1**, **Figure 2**, and **Figure 3**. More detailed methods and a summary of all findings are in eTable 11 in the Supplement. The full report with a detailed description of all findings including meta-analyses and detailed methods is available on the UK Food Standards Agency website (http://www.food.gov.uk/science/research/allergy-research/fs305005) together with an associated statement by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (http://cot.food.gov.uk/cotstatements).

Risk of Food Allergy and Allergic Sensitization

Fifteen intervention trials reported food allergy to any food or to milk, egg, or peanut separately in 10 304 participants. Seventeen trials reported allergic sensitization to any allergen, aeroallergen, food allergen, egg, peanut, or milk in 7310 participants. A summary of findings is shown in eTable 11 in the Supplement. Key findings for food allergy and allergic sensitization to egg, peanut, or milk are summarized in Figure 1, A and B.

Meta-analysis of 5 trials (1915 participants) showed evidence that egg introduction at 4 to 6 months was associated with lower risk of egg allergy compared with later egg introduction (risk ratio [RR], 0.56; 95% CI, 0.36-0.87; $P = .009$; moderate heterogeneity [$I^2 = 36\%$]).[6,15-18] Absolute risk reduction for a population with 5.4% incidence of egg allergy was 24 cases (95% CI, 7-35 cases) per 1000 population. Meta-analysis of 4 trials (1786 participants) showed no association between timing of egg introduction and egg sensitization.

Meta-analysis of 2 trials (1550 participants) showed evidence that peanut introduction at age 4 to 11 months was associated with lower risk of peanut allergy (RR, 0.29; 95% CI, 0.11-0.74; $P = .009$; high heterogeneity [$I^2 = 66\%$]).[4-6] Absolute risk reduction for a population with 2.5% incidence of peanut allergy was 18 cases (95% CI, 6-22 cases) per 1000 population. One trial (640 participants) reported significantly reduced allergic sensitization to peanut with early peanut introduction, but numerical data were not reported; a second trial (1168 participants) found no significant association (Figure 1B).[4,6]

For several key findings, there was moderate to high statistical heterogeneity. For the egg introduction and egg allergy analysis, heterogeneity was due to the abstract publication by Natsume and colleagues[17]—the authors declined to share further information about their study. The study by Perkin and colleagues,[6] which used multiple allergenic food introduction, had findings that were consistent with other studies[15,16,18] in which egg was the only allergenic food used. For the egg introduction and egg sensitization analysis, heterogeneity was due to the abstract publication by Bellach and colleagues,[16] which used specific IgE rather than skin prick testing to determine egg sensitization. For the peanut introduction and peanut allergy analysis, the high heterogeneity was attributed to the high treatment adherence in the study by Du Toit and colleagues[4] compared with more variable treatment adherence in the study by Perkin and colleagues.[6]

In interventional studies, there was no association between timing of introduction of cow's milk[19,20] (Figure 1) or other allergenic food and food allergy or allergic sensitization and no association between timing of introduction of one allergenic food and risk of food allergy or allergic sensitization to a different food (eTable 11 in the Supplement).

Abstract publications made a significant contribution to the analysis of egg introduction and egg allergy. However, the findings were similar in sensitivity analyses excluding abstract publications for which authors were unable to share full trial findings (eFigure 3A in the Supplement) or excluding studies at high or unclear risk of bias (eFigure 3B in the Supplement). In sensitivity analyses of allergic sensitization that excluded abstracts (eFigure 4A in the Supplement) or studies at high or unclear risk of bias (eFigure 4B in the Supplement), early egg introduction was associated with significantly reduced risk of allergic sensitization to egg.

Eighteen observational studies reported food allergy in 40 194 participants, and 20 studies reported allergic sensitization in 23 466 participants. One prospective cohort study (699 participants) found an association between early egg introduction and decreased egg allergy (odds ratio [OR], 0.29; 95% CI, 0.15-0.56) and adjusted for possible reverse causation.[21] Three cohort studies (13 472 participants), which could not be meta-analyzed because of statistical heterogeneity and heterogeneity of analysis methods (Figure 2A), found that early fish introduction (before age 6-9 months) was associated with reduced allergic sensitization to any allergen or food allergens.[22-24] There was no association between timing of introduction of other allergenic foods and risk of food allergy or allergic sensitization. Assessment for publication bias in analyses of food allergy and allergic sensitization was not possible because of the limited number of studies in each meta-analysis.

Table 1. Characteristics of Randomized Clinical Trials of Early vs Late Egg or Peanut Introduction and Risk of Egg or Peanut Allergy

Source	Country	Population	Intervention	No. of Participants		Outcomes Reported	Age at Outcome Assessment
				Early Introduction	Late Introduction		
Bellach et al,[16] 2016[a]	Germany	"Normal-risk" infants aged 4-6 mo with specific IgE to egg <0.35 kU/L	Pasteurized egg white powder (2.5 g protein) vs rice powder 3 times/wk from age 4-6 mo to 12 mo	184	199	Egg allergy diagnosed by oral food challenge plus specific IgE to egg ≥0.35 kU/L	1 y
Du Toit et al,[4,41] 2015, 2016	United Kingdom	"High-risk" infants aged 4 to 11 mo with moderate or severe eczema or egg allergy and peanut SPT <4 mm	Six g peanut protein/wk as peanut snack or peanut butter divided between ≥3 meals vs peanut avoidance from randomization to age 5 y	319	321	Peanut allergy diagnosed by oral food challenge	5 and 6 y
Halpern et al,[45] 1973[b]	United States	"Normal-risk" white infants seen at birth by 1 of 11 private pediatricians	Egg yolk given before age 3 wk vs after age 6 mo. No further details on dosing, form, or frequency available	~875	~875	Allergy to egg yolk defined as reproducible characteristic symptoms on ≥3 separate challenge feeds	7 mo
Natsume et al,[17] 2016[a]	Japan	"High-risk" infants with eczema by age 4-5 mo	Heated egg powder, 50 mg/d, from age 6-9 mo; 250 mg/d from age 9-12 mo vs placebo from age 6-12 mo	60	61	Egg allergy diagnosed by oral food challenge	1 y
Palmer et al,[15] 2013	Australia	"High-risk" singleton term infants with moderate or severe eczema (SCORAD ≥15) and no prior egg or solid food intake[c]	One tsp pasteurized whole egg powder daily (0.9 g protein) vs rice flour powder from age 4 mo to 8 mo	49	37	Egg allergy diagnosed by oral food challenge to pasteurized egg plus positive skin prick test	1 y
Palmer et al,[46] 2016[d]	Australia	"High-risk" infants with an atopic mother, no prior egg ingestion, and no prior allergic disease	Pasteurized whole egg powder daily (0.9 g protein) vs rice powder daily from age 4-6 mo to 10 mo	407	413	Egg allergy diagnosed by oral food challenge to pasteurized egg plus positive skin prick test	1 y
Perkin et al,[6] 2016	United Kingdom	"Normal-risk" singleton term infants exclusively breastfed for ≥3 mo	Sequential introduction of 6 allergenic foods aiming for 4 g protein/wk for each food, cow's milk (yogurt), then peanut, boiled egg, sesame, fish, and wheat from age 3 mo, vs avoidance to age ≥6 mo	652	651	Egg allergy and peanut allergy diagnosed by oral food challenge	1 and 3 y
Tan et al,[18] 2016	Australia	"High-risk" infants with first-degree relative with allergic disease and egg skin prick test <2 mm at age 4 mo	Pasteurized whole egg powder daily (350 mg egg protein) vs rice powder daily from the time of solid food introduction to age 8 mo	165	154	Egg allergy diagnosed by oral food challenge to lightly cooked whole egg	1 y

[a] Abstract publication; authors unable to share further details.

[b] Data not reported in a form that could be included in meta-analysis.

[c] Score ranges from 0 to 103, with higher scores indicating more severe eczema. Scoring Atopic Dermatitis (SCORAD) can be classified as mild (<15), moderate (15-40), and severe (>40) eczema.

[d] Study completed but not published at the time of the systematic review search, so not included in primary analyses but included in the post hoc trial sequential analysis.

Table 2. Risk of Bias and Directness of Evidence From Randomized Clinical Trials of Early vs Late Egg or Peanut Introduction and Risk of Egg or Peanut Allergy

Source	Breastfeeding at Randomization, No. (%)	Age at Randomization	Eczema Status at Enrollment, No. (%)[b]	Risk of Bias	Conflict of Interest	Indirectness of Evidence
Bellach et al,[16] 2016[a]	250 (65)	Mean, 4.7 mo	33 (8.5)	Unclear	Unclear	Population with no egg sensitization
Du Toit et al,[4,41] 2015, 2016	268 (42)	Mean, 7.8 mo	571 (89) Severe eczema; mean SCORAD, 34	Unclear; related to blinding of outcome assessment	Low	Population with severe eczema but no high-level peanut sensitization and high level of treatment adherence
Halpern et al,[45] 1973[c]	459 (26) (enrolled at birth)	Birth	0; Enrolled at birth	Unclear risk of selection, assessment, and attrition bias	Low	Specific form of egg and timing of introduction
Natsume et al,[17] 2016[a]	Unclear	Unclear	121 (100)	Unclear	Unclear	Population with eczema
Palmer et al,[15] 2013	71 (83)	4 mo	86% (100) Eczema; median SCORAD, 33	Low	Unclear due to support of authors by formula milk and egg industries	Population with moderate or severe eczema
Palmer et al,[46] 2016[d]	541 (66)	Median, 5.8 mo (early) and 5.9 mo (late)	0	Low	Low	Population with no eczema
Perkin et al,[6] 2016	1303% (100) Exclusively	Median, 3.4 mo	317 (24); Median SCORAD, 7.5	Unclear; related to blinding of outcome assessment	Low	Specific multiple allergenic food introduction schedule that was difficult to adhere to; intervention group underwent baseline skin prick test to exclude egg or peanut sensitization
Tan et al,[18] 2016	142% (45) Exclusively	Median, 3.8 mo	82 (26)	Low	Low	Population with no egg sensitization

[a] Abstract publication; authors unable to share further details.

[b] Score ranges from 0 to 103, with higher scores indicating more severe eczema. Scoring Atopic Dermatitis (SCORAD) can be classified as mild (<15), moderate (15-40), and severe (>40) eczema.

[c] Data not reported in a form that could be included in meta-analysis.

[d] Study completed but not published at the time of the systematic review search, so not included in primary analyses but included in the post hoc trial sequential analysis.

Risk of Allergic Rhinitis

Thirteen intervention trials (6333 participants) and 12 observational studies (25 147 participants) reported allergic rhinitis. A summary of findings is shown in eTable 11 in the Supplement. Four cohort studies (12 781 participants) (Figure 2B) found fish introduction before age 6 to 12 months was associated with reduced allergic rhinitis at age 4 years or younger (OR, 0.59; 95% CI, 0.40-0.87; high heterogeneity [I^2 = 59%]) or at age 5 to 14 years (OR, 0.68; 95% CI, 0.47-0.98).[22,23,25,26] In a sensitivity analysis excluding studies at high or unclear risk of bias (eFigure 5 in the Supplement), the association between early fish introduction and reduced allergic rhinitis at age 4 years or younger was not statistically significant. It was not possible to explain the heterogeneity in the fish introduction and allergic rhinitis analysis. In other intervention and observational studies, timing of allergenic food introduction was not associated with risk of allergic rhinitis. Assessment for publication bias in analyses of allergic rhinitis was not possible because of the limited number of studies in each meta-analysis.

Risk of Wheeze

Sixteen intervention trials (8433 participants) and 30 observational studies (65 601 participants) reported wheeze. A summary of findings is shown in eTable 11 in the Supplement. Three cohort studies (11 155 participants) found that fish introduction before age 8 to 12 months was associated with reduced recurrent wheeze at age 4 years or younger (OR, 0.72; 95% CI, 0.59-0.87; no heterogeneity [I^2 = 0%]).[23,25,27] However, 5 other studies (13 033 participants) found no association between timing of fish introduction and wheeze.[28-32] In other intervention and observational studies, there was no association between timing of allergenic food introduction and risk of wheeze. Assessment for publication bias in analyses of wheeze was not possible because of the limited number of studies in each meta-analysis.

Risk of Eczema

Seventeen intervention trials (6798 participants) and 37 observational studies (59 120 participants) reported eczema. A summary of findings is shown in eTable 11 in the Supplement. For most analyses of intervention trials, data were sparse; for several analyses of observational studies, statistical heterogeneity was high. Overall, there was no consistent association between timing of allergenic food introduction and risk of eczema from either intervention or observational studies. Assessment for publication bias in analyses of eczema was not possible because of the limited number of studies.

Risk of Autoimmune Diseases

Five intervention trials (5623 participants) and 48 observational studies (63 576 participants) reported autoimmune disease, and 2 other systematic reviews of observational data were identified. A summary of findings is shown in eTable 11 in the Supplement. The systematic reviews found no consistent evidence for an association between timing of gluten introduction and celiac disease.[33,34] Intervention trials also found no association between timing of gluten introduction and celiac disease (Figure 3) or type 1 diabetes mellitus or

Table 3. Summary of Key Review Findings for Early vs Late Introduction of Allergenic Food to the Infant Diet[a]

Dietary Exposure and Outcome	Study Design	Effect Estimate (95% CI)	Evidence GRADE	Cases per 1000 Population		No. Needed to Treat (95% CI)
				Control Risk	Risk Difference (95% CI)	
Egg introduction and egg allergy	6 RCTs n = 3665	RR, 0.56 (0.36-0.87)	Moderate	54 (Normal risk) 100 (High risk) 500 (Very high risk)	24 Cases fewer (7 fewer to 35 fewer) 44 Cases fewer (13 fewer to 64 fewer) 220 Cases fewer (65 fewer to 320 fewer)	42 (29-143) 23 (16-77) 5 (3-15)
Peanut introduction and peanut allergy	2 RCTs n = 1550	RR, 0.29 (0.11-0.74)	Moderate[b]	25 (Normal risk) 170 (High risk)	18 Cases fewer (6 fewer to 22 fewer) 121 Cases fewer (44 fewer to 151 fewer)	56 (45-167) 8 (7-23)
Fish introduction						
Allergic rhinitis	4 PCSs n = 12 781	Rhinitis at age ≤4 y: OR, 0.59 (0.40-0.87) Rhinitis at age 5-14 y: HR, 0.68 (0.47-0.98)	Low	Rhinitis at age ≤4 y: 50 (Normal risk) 100 (High risk) Rhinitis at age 5-14 y: 100 (Normal risk) 200 (High risk)	18 Cases fewer (6 fewer to 30 fewer) 38 Cases fewer (12 fewer to 57 fewer) 32 Cases fewer (2 fewer to 53 fewer) 64 Cases fewer (4 fewer to 106 fewer)	56 (33-167) 26 (18-83) 31 (19-500) 16 (9-250)
Allergic sensitization	5 PCSs n = 14 193	Any allergen: OR, 0.75 (0.64-0.88) Any food: OR, 0.52 (0.37-0.73)	Very low	Sensitization to any allergen: 200 (Normal risk) 400 (High risk) Sensitization to any food: 100 (Normal risk) 200 (High risk)	42 Cases fewer (20 fewer to 62 fewer) 67 Cases fewer (30 fewer to 101 fewer) 45 Cases fewer (25 fewer to 61 fewer) 85 Cases fewer (46 fewer to 115 fewer)	24 (16-50) 15 (10-33) 22 (16-40) 12 (9-22)
Gluten introduction and celiac disease	4 RCTs n = 1822	RR, 1.22 (0.81-1.83)	High	10 (Normal risk) 100 (High risk)	2.2 Cases more (1.9 fewer to 8.3 more) 22 Cases more (19 fewer to 83 more)	
Cow's milk introduction						
Type 1 diabetes mellitus	7 PCSs 1 NCCS 25 CCSs n = 42 858	Cow's milk at age ≤0-2 mo: OR, 1.20 (0.53-2.71) Cow's milk at age ≤3-4 mo: OR, 0.92 (0.75-1.13) Cow's milk at age ≤5-7 mo: OR, 1.88 (1.05-3.39)	Very low	Cow's milk at age ≤0-2 mo: 1 (Normal risk) 10 (High risk) Cow's milk at age ≤3-4 mo: 1 (Normal risk) 10 (High risk) Cow's milk at age ≤5-7 mo: 1 (Normal risk) 10 (High risk)	0.2 Case more (0.5 fewer to 1.7 more) 2 Cases more (4.7 fewer to 16.6 more) 0.1 Case fewer (0.2 fewer to 0.1 more) 0.8 Case fewer (2.5 fewer to 1.3 more) 0.9 Cases more (0.0 to 2.4 more) 8.6 Cases more (0.5 more to 23.1 more)	
Eczema	12 RCTs 1 qRCT 3 CCTs n = 6752	Eczema at age ≤4 y: RR, 1.14 (0.87-1.49) Eczema at age 5-14 y: RR, 1.05 (0.90-1.23)	Low	Eczema at age ≤4 y: 200 (Normal risk) 300 (High risk) Eczema at age 5-14 y: 50 (Normal risk) 100 (High risk)	28 Cases more (26 fewer to 98 more) 42 Cases more (39 fewer to 147 more) 3 Cases more (5 fewer to 12 more) 5 Cases more (10 fewer to 23 more)	
Wheeze	11 RCTs 1 qRCT 3 CCTs n = 7793	Wheeze at age ≤4 y: RR, 1.12 (0.77-1.62) Recurrent wheeze at age ≤4 y: RR, 1.18 (0.77-1.81)	Low	Wheeze at age ≤4 y: 200 (Normal risk) 300 (High risk) Recurrent wheeze at age ≤4 y: 100 (Normal risk) 200 (High risk)	24 Cases more (46 fewer to 124 more) 36 Cases more (69 fewer to 186 more) 18 Cases more (23 fewer to 81 more) 36 Cases more (46 fewer to 162 more)	

Abbreviations: CCS, case-control study; CCT, controlled clinical trial; HR, hazard ratio; NCCS, nested case-control study; OR, odds ratio; PCS, prospective cohort study; RCT, randomized clinical trial; qRCT, quasi randomized clinical trial; RR, risk ratio.

[a] Data are shown for all positive findings and for other findings for which meta-analysis of a significant number of studies and participants was possible. Number needed to treat is given only for outcomes where evidence of association was found. Risk difference is the absolute risk reduction for different control risks.

[b] GRADE of evidence increased because of strong effect size. Control risks are estimated from included studies or when relevant from other large, population-based studies for populations at different risks of the outcome.

Specifically, the risks of egg allergy refer to an unselected population of infants (normal risk), infants at high hereditary risk of allergic disease (high risk), and infants with moderate to severe eczema (very high risk); risks of peanut allergy refer to an unselected population of infants (normal risk) and infants with moderate to severe eczema (high risk); risks of allergic rhinitis, allergic sensitization, eczema, and wheeze refer to an unselected population of infants (normal risk) and infants at high risk of allergic disease due to having an affected first-degree relative (high risk); risks of celiac disease and type 2 diabetes mellitus refer to an unselected population of infants (normal risk) and infants at high risk of disease due to either having an affected first-degree relative having a high-risk genotype (high risk).

Table 4. GRADE of Evidence Assessment for Key Review Findings for Early vs Late Introduction of Allergenic Food to the Infant Diet[a]

Dietary Exposure and Outcome	Study Design[b]	Risk of Bias	Inconsistency	Indirectness	Imprecision
Egg introduction and egg allergy	6 RCTs n = 3665	Not serious; 1 study at high risk of bias, no studies at high risk of conflict of interest	Not serious; I^2 = 36% (P = .18); study estimates vary from 0.22 to 0.69 for the studies at low risk of bias	Serious; 3 studies recruited only infants without egg sensitization; 1 study only infants with eczema; 1 study used multiple allergenic foods	Not serious; 95% CI for RR is wide; trial sequential analysis suggests that optimum information size has not yet been reached
Peanut introduction and peanut allergy	2 RCTs n = 1550	Not serious; neither study at high risk of bias or conflict of interest	Not serious; I^2 = 66% (P = .09); study estimates vary from 0.49 to 0.19, but heterogeneity is likely to be explained by differences in participant adherence to the intervention	Serious; 1 study recruited only infants with egg allergy or eczema and without high-level peanut sensitization; 1 study used multiple allergenic foods	Serious; 95% CI for RR is wide
Fish introduction					
Allergic rhinitis	4 PCs n = 12 781	Not serious; 1 study at high risk of bias; all studies at low risk of conflict of interest	Not serious; I^2 = 59% (P = .09); study estimates vary from 0.45 to 0.77, but all 4 studies statistically significant, and heterogeneity was reduced when early-onset eczema cases were excluded from analysis because of potential reverse causation	Not serious; studies all undertaken in Scandinavia; 3 studies were in representative birth cohorts, 1 in a birth cohort selected for high risk of type 2 diabetes mellitus	Not serious; 95% CIs are wide but not close to 1, and together the 4 studies include >12 000 participants
Allergic sensitization	5 PCSs n = 14 193	Not serious; 2 studies with ~700 participants at high risk of bias; 3 studies (~13 000) at low risk of bias; no conflict of interest	Not serious; extreme heterogeneity for meta-analysis of inhalant sensitization; consistent findings for other sensitizations	Serious; allergic sensitization is an indirect measure of disease	Not serious; 3 studies at low risk of bias were consistent—ORs or HRs from 0.41 to 0.78—and included >13 000 participants
Gluten introduction and celiac disease	4 RCTs n = 1822	Not serious; 1 study at high risk of bias; all studies at low or unclear risk of conflict of interest	Not serious; I^2 = 46% (P = .13) due to 1 small study with high risk of bias; other estimates from 0.96 to 1.66	Not serious; 2 studies used only serology, but this surrogate is highly correlated with clinical disease; all participants had high risk genotype or family history	Not serious; significant benefit unlikely; lower bound of 95% CI, 0.81 or 0.85 excluding study at high risk of bias
Cow's milk introduction					
Type 2 diabetes mellitus	7 PCSs 1 NCCS 25 CCSs n = 42 858	Not serious; 12 studies at high overall risk of bias; all studies at low risk of conflict of interest	Serious; high or extreme statistical heterogeneity in several analyses; in some meta-analyses, significant associations were seen for retrospective but not for prospective studies	Not serious; all but 1 PC reported islet autoimmunity as a surrogate for type 2 diabetes mellitus; retrospective studies used clinical diagnosis	Not serious; studies included >40 000 participants; 95% CIs for meta-analyses of prospective studies were wide
Eczema	12 RCTs 1 qRCT 3 CCTs n = 6752	Serious; 8 studies at high risk of bias; 2 studies at high risk of conflict of interest	Not serious; I^2 = 0 to 54% for different analyses, with estimates ranging from 0.32 to 3.63	Serious; 4 studies had a multifaceted intervention; 5 compared cow's milk introduction with soya, another allergenic food	Not serious; 95% CIs were wide for some comparisons but overall, >6000 participants were included
Wheeze	11 RCTs 1 qRCT 3 CCTs n = 7793	Serious; 7 studies at high overall risk of bias; 2 studies at high risk of conflict of interest	Serious; I^2 = 0 to 59% for different analyses, with estimates ranging from 0.13 to 2.98; 2 meta-analyses showed significant effects not supported by other analyses	Not serious; 4 studies had a multifaceted intervention; 6 compared cow's milk introduction with soya; findings were consistent with a study of cow's milk introduction without soya	Not serious; 95% CIs were wide for some comparisons, but overall >6000 participants were included

Abbreviations: CCS, case-control study; CCT, controlled clinical trial; HR, hazard ratio; NCCS, nested case-control study; OR, odds ratio; PCS, prospective cohort study; RCT, randomized clinical trial; qRCT, quasi randomized clinical trial; RR, risk ratio.

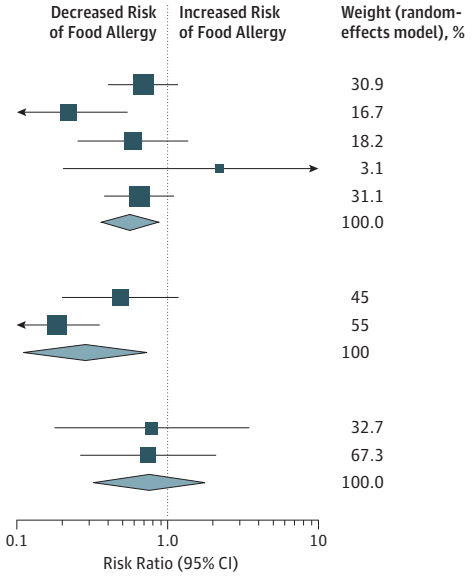
[a] GRADE assessments are shown for all positive findings and for other findings for which meta-analysis of a significant number of studies and participants was possible. Evaluation of publication bias was possible only for 1 outcome, timing of cow's milk introduction and type 2 diabetes mellitus; funnel plots were not asymmetrical and Egger test was not significant (P = .26 for milk introduction age ≤0-2 mo; P = .59 for milk introduction age ≤3-4 mo), suggesting no evidence of publication bias. For other analyses, there were insufficient studies to undertake formal testing of publication bias.

[b] The number of studies included is not always the same as the number of studies included in the meta-analysis since some studies did not report data in a form that could be included in meta-analyses. All data were considered when making GRADE assessments.

Figure 1. Early Allergenic Food Introduction and Risk of Food Allergy or Food Sensitization

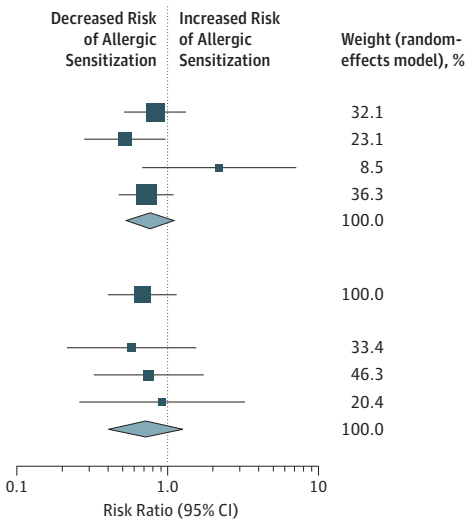
A Risk of food allergy

Outcome	Dietary Introduction of Allergenic Food: Early No. of Events	Early Total No.	Late No. of Events	Late Total No.	Risk Ratio (95% CI)	Weight (random-effects model), %
Egg allergy						
Perkin et al,[6] 2016	21	569	32	596	0.69 (0.40-1.18)	30.9
Natsume et al,[17] 2016	5	60	23	61	0.22 (0.09-0.54)	16.7
Tan et al,[18] 2016	8	130	13	124	0.59 (0.25-1.37)	18.2
Bellach et al,[16] 2015	2	142	1	156	2.20 (0.20-23.97)	3.1
Palmer et al,[15] 2013	14	42	18	35	0.65 (0.38-1.11)	31.1
Random-effects model Heterogeneity: I^2 = 35.8%; P = .18		943		972	0.56 (0.36-0.87)	100.0
Peanut allergy						
Perkin et al,[6] 2016	7	571	15	597	0.49 (0.20-1.19)	45
Du Toit et al,[4] 2015	10	312	54	313	0.19 (0.10-0.36)	55
Random-effects model Heterogeneity: I^2 = 66.1%; P = .09		883		910	0.29 (0.11-0.74)	100
Milk allergy						
Perkin et al,[6] 2016	3	569	4	597	0.79 (0.18-3.50)	32.7
Lowe et al,[19] 2011	6	193	8	191	0.74 (0.26-2.10)	67.3
Random-effects model Heterogeneity: I^2 = 0%; P = .95		762		788	0.76 (0.32-1.78)	100.0



B Risk of allergic sensitization

Outcome	Dietary Introduction of Allergenic Food: Early No. of Events	Early Total No.	Late No. of Events	Late Total No.	Risk Ratio (95% CI)	Weight (random-effects model), %
Egg sensitization						
Perkin et al,[6] 2016	29	568	37	599	0.83 (0.52-1.33)	32.1
Tan et al,[18] 2016	13	122	25	122	0.52 (0.28-0.97)	23.1
Bellach et al,[16] 2015	8	142	4	156	2.20 (0.68-7.14)	8.5
Palmer et al,[15] 2013	19	42	22	35	0.72 (0.47-1.09)	36.3
Random-effects model Heterogeneity: I^2 = 37%; P = .19		874		912	0.77 (0.53-1.11)	100.0
Peanut sensitization						
Perkin et al,[6] 2016	22	569	34	599	0.68 (0.40-1.15)	100.0
Milk sensitization						
Perkin et al,[6] 2016	6	568	11	599	0.58 (0.21-1.55)	33.4
Lowe et al,[19] 2011	9	178	12	178	0.75 (0.32-1.74)	46.3
Kjellman and Johansson,[20] 1979	4	25	4	23	0.92 (0.26-3.26)	20.4
Random-effects model Heterogeneity: I^2 = 0%; P = .84		771		800	0.72 (0.40-1.27)	100.0



Effect of early vs late dietary introduction of allergenic food (egg, milk, or peanut) on risk of food allergy (A) or allergic sensitization (B) to the same food. Data are from randomized clinical trials. "Event" refers to food allergy (A) or allergic sensitization (B) to the same food. The size of the data markers is proportional to study weights in the meta-analysis.

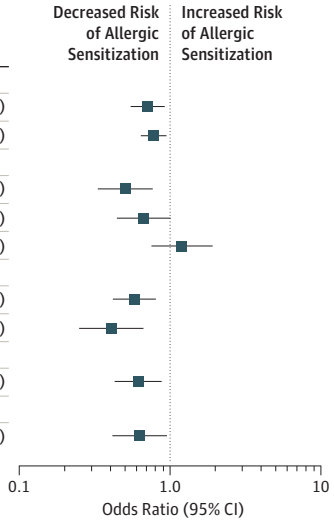
milk introduction and type 1 diabetes mellitus.[7,35-38] In sensitivity analyses excluding studies at high or unclear risk of bias (eFigure 6A in the Supplement) or only high risk of bias (eFigure 6B in the Supplement), there was no association between timing of gluten introduction and celiac disease. For the gluten introduction and celiac disease analysis, heterogeneity was due to the study by Sellitto and colleagues[37]—in this study, the control group had not yet ingested gluten at the time of outcome assessment so celiac disease or serology could not manifest.

Observational studies found no association between timing of gluten introduction and risk of celiac disease or inflammatory bowel disease; milk introduction and celiac disease or juvenile idiopathic arthritis; or timing of allergenic food

Figure 2. Early Fish Introduction and Risk of Allergic Sensitization or Rhinitis

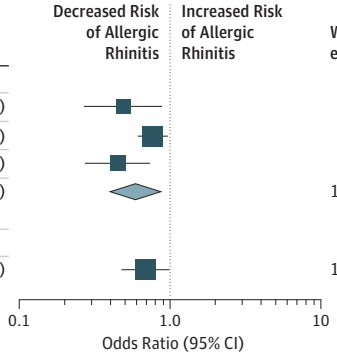
A Risk of allergic sensitization

Allergen	No. of Events	Total No.	Odds Ratio (95% CI)
Any allergen			
Nwaru et al,[26] 2013	1379	3675	0.71 (0.55-0.92)
Kull et al,[23] 2006	612	2545	0.78 (0.64-0.95)
Any aeroallergen			
Alm et al,[22] 2011	153	3481	0.50 (0.33-0.76)
Nwaru et al,[24] 2010	947	3675	0.66 (0.44-1.00)
Zutavern et al,[30] 2004	92	552	1.19 (0.74-1.89)
Any food			
Alm et al,[22] 2011	298	3636	0.59 (0.42-0.82)
Nwaru et al,[24] 2010	881	3675	0.41 (0.25-0.67)
Cow's milk			
Nwaru et al,[26] 2013	515	3675	0.63 (0.44-0.90)
Egg			
Nwaru et al,[26] 2013	368	3675	0.64 (0.42-0.97)



B Risk of allergic rhinitis

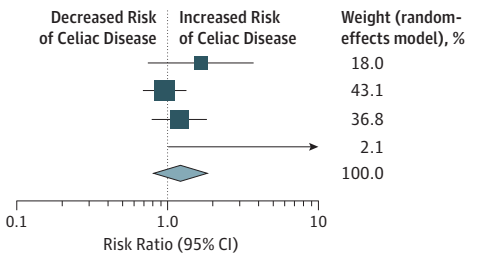
Source	No. of Events	Total No.	Odds Ratio (95% CI)	Weight (random-effects model), %
Age at outcome = birth to 4 y				
Alm et al,[22] 2011	246	4465	0.49 (0.27-0.89)	24.0
Kull et al,[23] 2006	373	3575	0.77 (0.61-0.97)	46.8
Nafstad et al,[25] 2003	98	2271	0.45 (0.27-0.74)	29.1
Random-effects model Heterogeneity: I^2 = 59.2%; P = .09			0.59 (0.40-0.87)	100
Age at outcome = 5 to 14 y				
Nwaru et al,[26] 2013	442	3112	0.68 (0.47-0.98)	100



Association between early dietary introduction of fish and different forms of allergic sensitization (A) or allergic rhinitis (B). Data are from observational studies. The size of the data markers in panel B is proportional to study weights in the allergic rhinitis meta-analysis. Age represents age at outcome assessment.

Figure 3. Early Gluten Introduction and Risk of Celiac Disease

Outcome	Dietary Introduction of Gluten: Early No. of Events	Early Total No.	Late No. of Events	Late Total No.	Risk Ratio (95% CI)
Beyerlein et al,[35] 2014	14	77	8	73	1.66 (0.74-3.72)
Lionetti et al,[36] 2014	53	328	64	379	0.96 (0.69-1.33)
Vriezinga et al,[7] 2014	44	475	36	465	1.20 (0.78-1.82)
Sellitto et al,[37] 2012	8	13	0	12	15.74 (1.01-245.35)
Random-effects model Heterogeneity: I^2 = 46.1%; P = .13		893		929	1.22 (0.81-1.83)



Effect of early vs late dietary introduction of gluten on risk of celiac disease. Data are from randomized clinical trials. "Event" refers to celiac disease. The size of the data markers is proportional to study weights in the meta-analysis.

introduction and risk of type 1 diabetes mellitus. There was no evidence of publication bias in analyses of milk introduction and type 1 diabetes mellitus (P = .26 and P = .59 by Egger test), and assessment for publication bias was not possible for other comparisons because of the limited number of studies in each meta-analysis.

GRADE Evaluation of Certainty of Findings

Key findings were affected by the study of select populations with either active allergic disease, absence of allergic sensitization to the intervention food, or both. There was also significant variation between the populations studied in each trial. Interventions varied from early short-term

(3-4 days) introduction of an allergenic food to early sustained introduction of single or multiple allergenic foods to trials of delayed allergenic food introduction and multifaceted studies that also included other dietary components, often together with environmental control measures such as tobacco smoke and house dust mite avoidance. GRADE of evidence was therefore reduced in several analyses because of indirectness of the population or intervention (Table 4). GRADE of evidence for the egg and peanut findings was also reduced because of imprecise effect estimates but was increased for peanut because of the strong effect size seen in the trial of Du Toit and colleagues.[4]

Trial Sequential Analysis of Moderate- or High-Certainty Findings

Peanut introduction and peanut allergy were not evaluated using trial sequential analysis because of insufficient data in the meta-analysis to estimate a sufficient number of points for the monitoring boundaries. There were also insufficient data to perform trial sequential analysis for 10% or 20% relative risk reduction for other findings. Whether early egg introduction was associated with a 30% reduction in risk of egg allergy using trial sequential analysis was assessed. The heterogeneity-adjusted and unadjusted optimal information sizes for detection of a 30% relative risk reduction for egg allergy were 8643 and 5239 study participants, respectively. Trial sequential analysis for this outcome is shown in eFigures 7A and 7B in the Supplement. Although the conventional line of statistical significance was crossed (z = 1.96) in both analyses, the optimal information size was not reached in either case. The cumulative z score did not cross the monitoring boundary, although it is close in unadjusted trial sequential analysis. It cannot be confidently concluded that early egg introduction reduces egg allergy by at least 30%; further trials are required to quantify the treatment effect.

Trial sequential analysis was also used to evaluate whether early gluten introduction increases celiac disease risk by 30%. The heterogeneity-adjusted and unadjusted optimal information sizes for detection of a 30% increase in relative risk of celiac disease were 3599 and 9497 study participants, respectively. Trial sequential analysis for this outcome is shown in eFigures 7C and 7D in the Supplement. The conventional line of statistical significance was not crossed and the optimal information size was not reached. The cumulative z score was close to the line of futility in unadjusted trial sequential analysis. It cannot be confidently concluded that further studies of timing of gluten introduction and risk of celiac disease are futile.

Discussion

This systematic review found evidence that timing of introduction of certain allergenic foods to the infant diet was associated with risk of allergic disease but not risk of autoimmune disease. There was moderate-certainty evidence that introduction of egg to the infant diet at age 4 to 6 months was associated with reduced egg allergy and introduction of peanut at age 4 to 11 months was associated with reduced peanut allergy compared with later introduction of these foods. There was low-certainty evidence that fish introduction before age 6 to 12 months was associated with reduced allergic rhinitis and very low-certainty evidence that fish introduction before age 6 to 9 months was associated with reduced allergic sensitization.

The evidence base for a relationship between early allergenic food introduction and food allergy to the same food was limited to a relatively small number of studies and events and was only statistically significant for egg and peanut. Heterogeneity-adjusted trial sequential analysis of early egg introduction for egg allergy suggests that further trials are warranted to confirm the findings and quantify the magnitude of the treatment effect. Heterogeneity for egg introduction was attributable to 1 small study presented in abstract form only.[13] Trial sequential analysis without adjustment for heterogeneity showed stronger evidence that early egg introduction reduced risk of egg allergy by 30% or more but without crossing the trial sequential monitoring boundary. Trial sequential analysis of early peanut introduction for peanut allergy was not possible due to the small number of studies and events in this analysis. The inability to undertake trial sequential analysis for this outcome emphasizes the value of further intervention studies of peanut introduction and peanut allergy.[39]

These findings are consistent with a large body of experimental data in various animal models in which early enteral antigen exposure is established as effective for preventing allergic sensitization to the same antigen.[40] This phenomenon of oral tolerance has not been directly shown to occur in humans until recently.[4,41] Oral tolerance in humans appears to be antigen specific, with no data showing early introduction of one allergenic food influences the development of allergy to a different allergenic food.

In contrast to egg and peanut allergy, this review found that oral tolerance was not relevant to celiac disease, suggesting that the findings may not be generalizable beyond food allergy mediated by IgE antibodies. Trial sequential analysis of gluten introduction and celiac disease risk found that further trials would not be futile; however, available data show no evidence of an association. Ongoing work is evaluating a potential role for oral tolerance in other autoimmune diseases; for example, the induction of immune tolerance to insulin for preventing type 1 diabetes mellitus.[42] There was also no consistent evidence that early cow's milk introduction influences risk of type 1 diabetes mellitus, which is consistent with recent literature; for example, a trial of extensively hydrolyzed vs intact infant formula showed no effect on type 1 diabetes mellitus risk.[43]

There was lower-certainty evidence that early fish introduction was associated with reduced allergic sensitization or rhinitis. Sensitivity analysis of studies at low risk of bias found that the association with allergic rhinitis at age 4 years or younger was not statistically significant. One plausible biological mechanism is that early exposure to the anti-inflammatory effects of omega-3 polyunsaturated fatty acids present in fish might influence development or expression of allergic sensitization and associated inflammatory disease.[44]

These data conflict with previous recommendations to delay introduction of allergenic foods to the infant diet and suggest that current guidelines that do not advise early introduction of allergenic foods may need to be revised.[1-3] They are, however, consistent with 1 recent intervention trial and a consensus statement regarding introduction of peanut to the infant diet,[4,5] and any differences in conclusions from other trials can be explained by the increased statistical power derived from meta-analysis.

Despite the comprehensive approach used in this review, it was not possible to exclude clinically important effects in most analyses because there were few studies. Certainty of evidence was downgraded because of imprecision and indirectness and variation in interventions used and populations studied. However, there was not a clear difference in outcome among studies of different populations in our analyses; for example, in meta-analysis of egg introduction and egg allergy, 3 studies undertaken in normal-risk, high-risk, and very high-risk populations had similar findings. Risk-of-bias assessment used different instruments for intervention and observational studies, which may not be directly comparable.

These systematic review findings should not automatically lead to new recommendations to feed egg and peanut to all infants. The imprecise effect estimates, issues regarding indirectness, and inconclusive trial sequential analysis findings all need to be considered, together with a careful assessment of the safety and acceptability of early egg and peanut introduction in different populations.

Conclusions

In this systematic review, early introduction of egg or peanut to the infant diet was associated with lower risk of developing egg or peanut allergy. These findings must be considered in the context of limitations in the primary studies.

ARTICLE INFORMATION

Author Contributions: Dr Boyle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ierodiakonou and Garcia-Larsen contributed equally to the manuscript.
Concept and design: Garcia-Larsen, Geoghegan, Leonardi-Bee, Boyle.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ierodiakonou, Garcia-Larsen, Groome, Chivinge, Geoghegan, Reeves, Tagiyeva, Boyle.
Critical revision of the manuscript for important intellectual content: Ierodiakonou, Garcia-Larsen, Logan, Cunha, Robinson, Geoghegan, Jarrold, Nurmatov, Trivella, Leonardi-Bee, Boyle.
Statistical analysis: Ierodiakonou, Garcia-Larsen, Chivinge, Geoghegan, Jarrold, Trivella, Leonardi-Bee.
Administrative, technical, or material support: Garcia-Larsen, Cunha, Chivinge, Geoghegan, Reeves, Nurmatov, Boyle.
Study supervision: Garcia-Larsen, Nurmatov, Boyle.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Ierodiakonou, Garcia-Larsen, Cunha, Tagiyeva-Milne, Nurmatov, Leonardi-Bee, and Boyle reported receiving support from the UK Food Standards Agency for the submitted work. Dr Boyle reported receipt of consultancy fees from Imperial Consultants for the work. No other disclosures were reported.

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